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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,453	07/11/2003	Avshalom Caspi	960296.99497	5194

7590  
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12/20/2007

EXAMINER
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SWITZER, JULIET CAROLINE

ART UNIT	PAPER NUMBER
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1634

MAIL DATE	DELIVERY MODE
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12/20/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

Application No.

10/617,453

Applicant(s)

CASPI ET AL.

Examiner

Juliet C. Switzer

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 19 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-3, 6 and 9-11 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 6, 9-11 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
- Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☒ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_.

**DETAILED ACTION**

***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/19/07 has been entered.

2. The amendments and arguments presented in the papers have been carefully considered but are not persuasive to place the application in condition for allowance for the reasons set forth in this office action.

***Claim Rejections - 35 USC § 112***

3. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a rejection for new matter.

The amended claim recites that "childhood maltreatment" is selected from exposure to psychological trauma and exposure to psychosocial stress.

The claim previously set forth these psychological trauma and exposure to psychosocial stress as potential pathogenic risk factors but not as types of childhood maltreatment, per se.

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The specification teaches that childhood maltreatment was assessed by observing mother-child interactions, measuring harsh discipline, measuring changes in primary care giver, assessing exposure to child physical abuse, and assessing unwanted sexual contact (§ 0042). The specification does not teach that the general categories psychological trauma and exposure to psychosocial stress are types of childhood maltreatment.

The response does not provide basis for the claim, and the examiner was not able to identify basis.

4. Claims 1, 2, 3, 6, and 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of assessing a human subject for a predisposition to conduct disorder, committing a violent offense, a disposition towards violence or symptoms antisocial behavior, the method comprising the steps of

determining whether the subject carries a two or three repeat allele of a variable number tandem repeat polymorphism within the gene encoding human monoamine oxidase A enzyme, wherein the locus of said promoter is amplified using instant SEQ ID NO: 1 and SEQ ID NO: 2,

determining whether the subject has experienced childhood maltreatment, and

concluding that the subject is predisposed to conduct disorder, committing a violent offense, a disposition towards violence or symptoms antisocial behavior, if the subject carries the a two or three repeat allele and if the subject has experienced the environmental risk factor, does not reasonably provide enablement for methods which determine whether the subject is at risk for experiencing the childhood maltreatment.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are sufficiently broad so as to encompass drawing a conclusion in an individual based on their "risk of experiencing" childhood maltreatment. The claims encompass testing of individuals of any age. For the testing of an adult, the risk of experiencing childhood maltreatment is moot, since that risk will have past. Every child, however, is at some risk of experiencing childhood maltreatment, whether it is a high risk or a low risk. Thus, the scope of the claim is sufficiently broad so as to encompass concluding that any child who carries the two or three repeat allele is predisposed to the phenotype. The specification has taught, however, there is no conclusive association between a "low activity" MAOA allele (that is the two or three repeat alleles) and violent or anti-social behavior (§ 0023).

The nature of the invention requires the knowledge of an association between the two or three allele of the MAOA and the conclusion that the subject is predisposed to the phenotype since every child is at risk of experiencing childhood maltreatment.

The specification does not provide any working examples where the method of the claimed invention is actually practiced, that is, where the method is used to assess the predisposition of an individual. The specification, however, exemplifies a relationship between one possible environmental risk factor, namely childhood maltreatment in males, and the mental disorder phenotypes conduct disorder, committing a violent offense, a disposition towards violence or symptoms antisocial behavior (see pages 11-16 of the specification). These pages of the specification focus exclusively on a relationship that involves the examination of a single

polymorphic location, that is a polymorphism variable number tandem repeat polymorphism that is known to effect expression. The examples only consider individuals who have actually experienced childhood maltreatment, they do not establish or study the relationship between "risk" of childhood maltreatment (any level of risk) and genotype/phenotype.

There is a high degree of unpredictability regarding the association of polymorphisms within the MAOA enzyme encoding gene and mental disorder phenotypes. The state of the prior art does not provide any data or evidence regarding another association that is "conditioned" by a particular risk factor. The prior art does however demonstrate many instances where practitioners attempted to establish relationships between polymorphisms within MAOA and mental disorder phenotypes and failed. For example, Wei et al. teach that they observed no significant differences in frequency of alleles a microsatellite repeat in MAOA between controls and subjects with schizophrenia (Wei et al. Eur Psychiatry 1998, Vol. 13, pages 407-410). Hamilton et al. (Molecular Psychiatry, 2000, Vol. 5, pages 465-466) teach that they found no genetic linkage or association between a polymorphism in the MAOA promoter and panic disorder. Norton et al. studied a single nucleotide polymorphism and a VNTR polymorphism in the MAOA gene and found no evidence for association with schizophrenia (Norton et al. American Journal of Medical Genetics (Neuropsychiatric Genetics) 2002, 114:491-496). Additional attempts were made to associate genotypes of the MAOA gene with completed suicides, manic-depressive illness, bipolar disorder, and unipolar disorder, but these were unsuccessful (Ono et al. American Journal of Medical Genetics (Neuropsychiatric Genetics) 2002, 114:340-342; Parsian et al. American Journal of Medical Genetics (Neuropsychiatric Genetics) 1997, 74:475-479; and Kung'u et al. Molecular Psychiatry, 1999, Vol. 4, 393-395).

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These studies together exemplify the high degree of unpredictability in this subject area.

Further, as previously noted, the instant specification even teaches that there is no association between the low activity MAOA alleles and violent behavior in the general population, yet the claims are sufficiently broad so as to imply such a relationship.

Thus, having carefully considered all of these factors, it is concluded that the specification is not sufficient to enable one to make and use the invention commensurate in scope with the instant claims.

### **Response to Remarks**

Applicant traverses the 112 1st rejection for scope of enablement.

Applicant points out that the art is familiar with behaviors that when experienced during childhood by a human subject would place that subject at risk for experiencing childhood maltreatment, and that one important point of the inventor's work was to show the specific confirmatory relationship between such experience (referring to risk for experiencing childhood maltreatment) and the mental disorder phenotype in subjects having the indicated genotype. However, this statement is not supported by the evidence on the record. Applicant only examined subjects that were classified as having experienced childhood maltreatment, not that were classified as at risk for childhood maltreatment.

Applicant state that because the data show the relationship in subjects who have experienced childhood maltreatment, one can logically conclude that if subjects at risk for experiencing childhood maltreatment were allowed to be maltreated and carried the indicated genotype, they to would be predisposed to a mental disorder phenotype. This argument is not commensurate in scope with the claim, given that it is based on the predisposition of those who

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are actually maltreated. As noted in the rejection, the scope of the claim is broad enough to include any risk or maltreatment, no matter how small, and this effectively includes all children. The specification makes it clear that the relationship between low activity MAOA and violence has not been shown to be true for all people.

The rejection is applied to the amended claims.

### ***Conclusion***

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.


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Juliet C. Switzer  
Primary Examiner  
Art Unit 1634

December 18, 2007